Br. J. clin. Pharmac. (1990), **29**, 525–531

The abnormal *in vitro* response to aspirin of platelets from aspirin-sensitive asthmatics is inhibited after inhalation of nedocromil sodium but not of sodium cromoglycate

C. H. MARQUETTE, M. JOSEPH, A. B. TONNEL, H. VORNG, P. LASSALLE, A. TSICOPOULOS & A. CAPRON

Centre d'Immunologie et de Biologie Parasitaire (Unité mixte INSERM 167 – CNRS 624), Institut Pasteur, Lille, France

1 Blood platelets from patients with aspirin-sensitive asthma (ASA) generated cytotoxic mediators in the presence of aspirin. This abnormal *in vitro* response to aspirin was abolished within 1 h after nedocromil sodium inhalation but not after sodium cromoglycate inhalation.

2 Platelets recovered this reactivity to aspirin by 12 hours after nedocromil sodium treatment of ASA-patients.

3 The *in vitro* reactivity to aspirin of ASA platelets isolated before inhalation was inhibited in the presence of serum isolated 15 and 60 min after nedocromil sodium inhalation.

Keywords aspirin-sensitive asthma platelets nedocromil sodium inhibition

Introduction

Aspirin-sensitive asthma (ASA) is characterized by the occurrence of bronchospasm following the ingestion of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) which, though antigenically unrelated, share the common property of being cyclo-oxygenase inhibitors (Szczeklik *et al.*, 1983). ASA affects 5 to 10% of asthmatics and occurs most frequently in middle-aged subjects (Slepian *et al.*, 1985; Spector & Farr, 1983).

Although this disorder was recognized at the beginning of this century, its pathophysiology remains a mystery. Several authors have attempted to understand the mechanisms responsible for this disorder and to achieve therapeutic results in inhibiting aspirin-induced bronchospasm (Baldochi *et al.*, 1983; Basomba *et al.*, 1976; Danker and Wedner, 1983; Delaney, 1976, 1983; Martin & Culver, 1983; Pleskow *et al.*, 1982; Stevenson *et al.*, 1983; Szczeklik *et al.*, 1980). We have previously demonstrated that *in vitro*, platelets from aspirin-sensitive asthmatics (ASA-patients) released cytotoxic mediators and oxygen-derived free radicals in the presence of aspirin and other cyclo-oxygenase inhibiting NSAIDs, whereas platelets from normal donors or from allergic asthmatics were unresponsive to these drugs (Ameisen *et al.*, 1985). This abnormal response to aspirin is restricted to platelets. Basophils from ASA-patients do not release histamine in the presence of aspirin. Monocytes, which can be triggered by IgE-dependent stimuli, do not express cytotoxic properties nor any burst of chemiluminescence in the presence of aspirin. Various experiments have excluded the involvement of immunological mechanisms in aspirin-dependent platelet activation. In fact, this abnormal cellular activation appeared to depend upon the inhibition of prostaglandin synthesis and could be prevented *in vitro* by the addition of prostaglandin endoperoxide or by preincubation with sodium salicylate, or salicylamide (Ameisen *et al.*, 1985, 1986c). Even if the involvement of platelet abnormalities in aspirin intolerance has not been definitely ascertained, the platelet activation test seems to represent a good reflection of the disease

activity: for example, after 'desensitization' of patients with aspirin at a daily dose of 600 mg, aspirin-induced platelet activation was suppressed as long as aspirin intake was continued (Martin & Culver, 1983).

Though 'desensitization' can be achieved by daily intake of aspirin (Pleskow *et al.*, 1982; Stevenson *et al.*, 1983), the severity of asthma is not dramatically lessened, and aspirin 'tolerance' tends to decline after several weeks (Baldochi *et al.*, 1983; Danker & Wedner, 1983; Martin & Culver, 1983). In this context it was of interest to test the efficacy of some anti-allergic drugs. Two drugs, ketotifen, a histamine (H_1)-receptor antagonist, and sodium cromoglycate, a mast cell-stabilizing agent, have been evaluated, but with little success (Basomba *et al.*, 1976; Delaney, 1976, 1983; Szczeklik *et al.*, 1980). Nedocromil sodium is a disodium salt of a pyranoquinoline dicarboxylic acid which has been recently developed as a novel treatment for reversible obstructive airways disease. Our aim was to investigate its potential effectiveness in ASA. We have reported (Thorel *et al.*, 1987) that nedocromil sodium inhibited *in vitro* the abnormal response of ASA-platelets at concentrations (10^{-9}M) which could be achieved in the plasma after inhalation of 4 mg of the drug (Auty & Clarke, 1986), whereas sodium cromoglycate only exerted an inhibiting effect at much higher concentrations (10^{-6}M), which could not be obtained *in vivo* by this route. In fact, platelet-mediated cytotoxicity in the presence of aspirin was dose-dependently inhibited by *in vitro* preincubation for 30 min with nedocromil sodium (ID_{50} = 2.10^{-10}M) or with sodium cromoglycate (ID_{50} = 2.10^{-7}M). Maximum inhibition with nedocromil sodium occurred at a concentration of 10^{-7}M, and of 10^{-6}M with sodium cromoglycate. Because of serious reactions (severe bronchospasm, angiiœdema) occasionally observed during aspirin challenge it was ethically unfeasable to evaluate the preventive effect of nedocromil sodium on aspirin-induced bronchospasm. Therefore we investigated, and report here the effect of nedocromil sodium (Tilade®) and of sodium cromoglycate (Lomudal®) *ex vivo* on the *in vitro* reactivity of ASA-platelets after inhalation of either drug.

Methods

Patients

Sixteen aspirin-sensitive asthmatics (nine males, seven females; aged 20–67 years) entered the study. The diagnosis of aspirin-sensitive asthma was made by the following criteria: (1) a typical clinical history of adverse bronchospastic reactions to cyclo-oxygenase inhibiting NSAIDs; and (2) a fall of forced expiratory volume in 1 s (FEV_1) of greater than 30%, 20 to 120 min following oral challenge with a low dose (less than 100 mg) of aspirin. In addition, all patients had a positive (greater than 30% cytotoxicity) aspirin-dependent platelet cytotoxicity assay (see below).

Platelet isolation

This procedure has been described in detail elsewhere (Ameisen *et al.*, 1985). Briefly, various blood samples were collected on ACD-C (ACD-C 1 vol/Blood 6 vol) and used within a period of 2 to 3 h. After counting under phase contrast microscopy, platelets were resuspended in Eagles minimum essential medium (MEM) and adjusted to the adequate concentration. Each time a patient was bled for platelet isolation an additional sample was collected for serum (hereafter referred as the 'corresponding serum').

Reagents

Acetylsalicylic acid (Catalgin®) was obtained from Theraplix Laboratories (Paris, France) and nedocromil sodium and sodium cromoglycate from Fisons plc (Loughborough, UK).

Aspirin-dependent platelet cytotoxicity assay (platelet activation test)

As previously described (Ameisen *et al.*, 1985), 150 × 10^6 platelets suspended in MEM were incubated with 50 to 100 *Schistosoma mansoni* larvae (schistosomula) in flat-bottomed microplates (Nunc, Roskilde, Denmark) in a final volume of 200 µl MEM. The patient serum at the final concentration of 10% was added 30 min before aspirin (0.6 mM). After 24 h at 37° C and 5% CO_2 in air, motionless and dark dead larvae were clearly distinguished from mobile and refringent living schistosomula by optical microscopy. Baseline cytotoxicity was defined as the percentage of dead schistosomula in the presence of aspirin minus the percentage of dead schistosomula in the absence of aspirin (control). Relative cytotoxicity at time x after inhalation of sodium cromoglycate or nedocromil sodium was defined as the ratio 'cytotoxicity at time x after inhalation of sodium

cromoglycate or nedocromil sodium/baseline cytotoxicity'. Inhibition of platelet cytotoxicity at time x after inhalation of sodium cromoglycate or nedocromil sodium was defined as following: '(1-cytotoxicity at time x after inhalation of sodium cromoglycate or nedocromil sodium/baseline cytotoxicity) × 100'.

Ex vivo *effect of nedocromil sodium and sodium cromoglycate on aspirin-dependent platelet cytotoxicity*

To determine whether nedocromil sodium and sodium cromoglycate could exert an effect *in vivo* on the abnormal platelet response to aspirin, platelets and sera were sampled before and after administration of the drugs by metered-dose inhaler (two puffs of 2 mg of nedocromil sodium, or one puff of 5 mg of sodium cromoglycate—Lomudal 5®—or one puff 20 mg sodium cromoglycate—Lomudal 20®). Platelets and corresponding serum sampled at sequential times before and after drug administration ($t0$ = just prior to drug inhalation; $t15$, $t60$ and $t120$ are equal to, respectively, 15, 60, and 120 min after drug inhalation) were incubated with aspirin and *S. mansoni* larvae. The cytotoxicity assay to measure platelet reactivity was performed as described above.

We also investigated separately the effect of nedocromil sodium inhalation directly on platelet reactivity to aspirin, and the possible inhibitory effect of the sera recovered at the same time in order to show a direct modification of platelets or an indirect effect consecutive to the level of nedocromil sodium present in the plasma after nedocromil sodium inhalation.

Therefore the platelet activation assay was performed by incubating the patient serum collected before nedocromil sodium inhalation ('nedocromil sodium free serum'), along with the patient platelets collected at sequential times after nedocromil sodium inhalation ($t15$, $t60$). Secondly, in investigating the inhibiting effect of serum after nedocromil sodium challenge, platelets isolated at $t0$ were incubated in the presence of serum sampled at $t15$, $t60$.

In order to investigate the effect of cumulative nedocromil sodium intake, patients continued taking 4 mg of nedocromil sodium (provided by a metered dose inhaler) four times a day for 1 week. Platelet and serum sampling were performed before and after the morning's nedocromil sodium inhalation on day 7, as on day 1. Time zero on day 7 ($t0$) was approximately 12 h after the last nedocromil sodium inhalation on the previous day.

Plasma concentration of nedocromil sodium

Plasma concentrations of nedocromil sodium were measured by radioimmunoassay before ($t0$) and at various times ($t15$ to $t240$) after nedocromil sodium inhalation.

Statistical methods and presentation of data

Significant differences between data were determined by either Student's paired or unpaired t-test or analysis of variance, as indicated. Results are reported as mean ± s.e. mean values unless indicated otherwise.

Results

Ex vivo *study. Modulation of aspirin-dependent platelet activation after inhalation of nedocromil sodium and sodium cromoglycate*

Baseline ($t0$) platelet aspirin-dependent activation (as measured by killing of *S. mansoni* larvae) was present in all patients (mean cytotoxicity: 58 ± 5.45%).

A dramatic inhibition of platelet cytotoxicity was achieved 15 min ($t15$) after inhalation of nedocromil sodium (mean inhibition: 70.8 ± 8.18%) in all patients but two. In these two patients inhibition was achieved subsequently at $t60$ (81.3% and 85.0% inhibition). Sixty minutes ($t60$) after nedocromil sodium challenge inhibition was even more prominent (mean inhibition: 86.5 ± 4.60%). Inhibition then slowly decreased with time: mean inhibition: 72.7 ± 10.6% and 57.2 ± 7.10% respectively at $t120$ and $t180$. In one patient tested 6 and 8 h after nedocromil sodium challenge, residual inhibition was respectively 47% and 17%. No significant inhibition could be obtained after sodium cromoglycate inhalation (Figure 1).

Aspirin-dependent platelet cytotoxicity measured at time zero ($t0$) on day 7 did not differ significantly from that measured at $t0$ on day 1 (t-paired test; $P = 0.21$; 8df) except in two patients whose platelets no longer responded to aspirin-dependent activation. One of them had a detectable plasma trough level of nedocromil sodium (0.3 ng ml^{-1}); the other not. Subsequent platelet inhibition ($t15$, $t60$, $t120$) followed a decreasing pattern similar to the one noted 7 days earlier.

Comparison of (1) aspirin-dependent cytotoxicity of platelets incubated in presence of the corresponding serum, (2) aspirin-dependent cytotoxicity of platelets collected at $t15$ incubated in presence of serum collected at $t0$

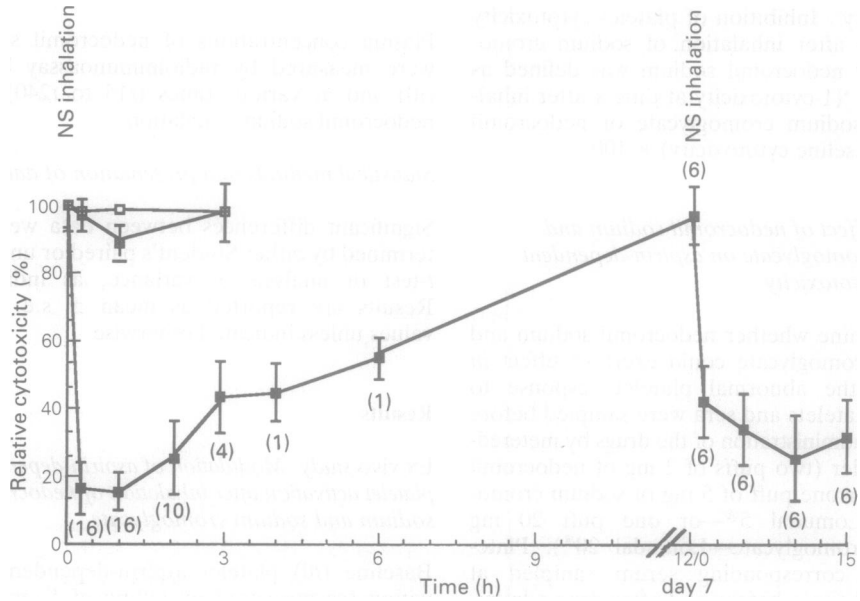

Figure 1 Platelet reactivity to aspirin after inhalation of nedocromil sodium 4 mg (■); sodium cromoglycate 5 mg (□), and sodium cromoglycate 20 mg (⊞). Platelet reactivity is expressed as relative cytotoxicity mean value ± s.e. mean. The number between brackets indicates the number of patients studied.

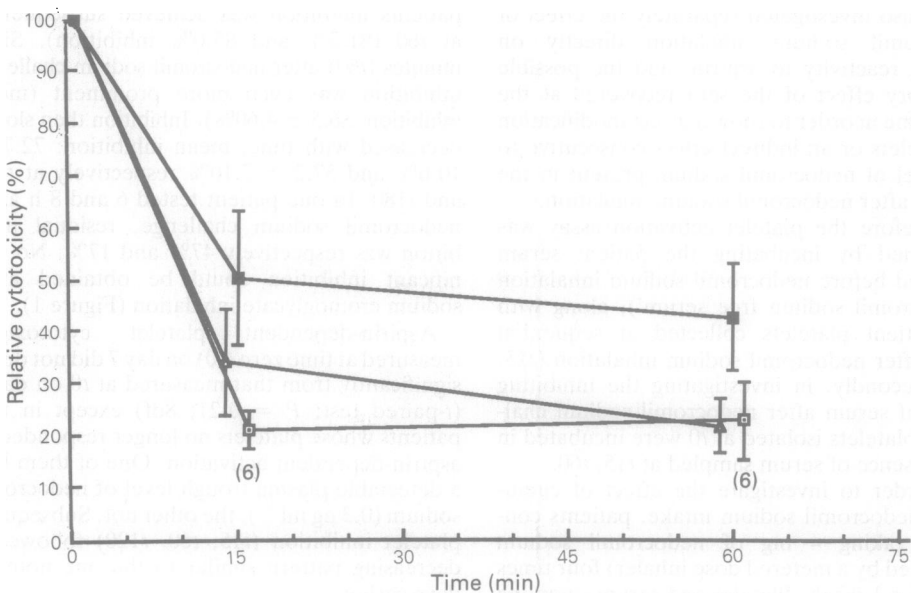

Figure 2 Modulation of platelet reactivity to aspirin after nedocromil sodium inhalation. (□ = platelets with corresponding serum; △ = platelets with nedocromil sodium free serum; ■ = platelets before nedocromil sodium inhalation with serum after nedocromil sodium inhalation.). Platelet reactivity is expressed as relative cytotoxicity mean value ± s.e. mean. The number between brackets indicates the number of patients studied.

(free of nedocromil sodium), and (3) aspirin-dependent cytotoxicity of platelets collected at *t*0 (before any intake of nedocromil sodium) incubated in presence of serum collected at *t*15 did not show any statistically significant difference ($F = 2.20$; F_{18}^2). The same comparison at *t*60 did not either show significant difference ($F = 2.20$; F_{18}^2). Thus, first, after inhalation of 4 mg of nedocromil sodium, platelets were inhibited to a similar degree in the presence or in the absence of the corresponding serum; and second, the small amount of nedocromil sodium present in the serum after inhalation of 4 mg of the drug was sufficient to inhibit aspirin-dependent platelet activation (Figure 2).

Plasma concentration of nedocromil sodium

Plasma concentrations reached 1.7 ± 0.33 ng ml^{-1}; 1.5 ± 0.31 ng ml^{-1} and 0.9 ± 0.19 ng ml^{-1} respectively 15, 60 and 120 min after nedocromil sodium inhalation. Trough concentrations (*t*0 = 12 h after the last two puffs on day 6) were below the limit of detection (i.e. < 0.25 ng ml^{-1}) except in one patient (0.3 ng ml^{-1}) whose platelets were no longer reactive to aspirin. Plasma concentrations measured after nedocromil sodium inhalation on day 7 followed a pattern of decrease similar to the one observed on day 1. We could not establish a linear correlation between plasma concentrations and the degree of platelet inhibition. However, nedocromil sodium inhalation was invariably followed by a dramatic fall in platelet reactivity to aspirin.

Tolerance

Nedocromil sodium was well tolerated in all patients but one. This patient discontinued nedocromil sodium inhalation because of coughing following each inhalation.

Discussion

Investigations regarding cell interactions in asthma have recently led to reconsideration of the involvement of non mast-cells (such as eosinophils, macrophages and platelets) in the mechanism of asthma. Demonstration of the existence of a specific receptor for the Fc fragment of the IgE ($Fc_{epsilon}$ R_{II}) on the membrane of these cells reinforced this hypothesis (Capron *et al.*, 1986) and offered new perspectives for research on mechanisms and regulation of asthma.

In allergic asthma IgE-dependent activation of platelets specifically triggered by the corresponding allergen occurs (Capron *et al.*, 1987). There is also evidence from lung washing studies of non-specific platelet activation within the airways after allergen provocation (Metzger *et al.*, 1985). Other investigations have indicated that exercise-induced asthma is associated with an increase in release of platelet-derived products similar to that observed in antigen induced asthma (Johnson *et al.*, 1986). Moreover, in ASA a direct, non-IgE-mediated abnormal response of platelets to NSAIDs has been demonstrated (Ameisen *et al.*, 1986b). All these observations support the concept of a potential role for platelets in asthma.

One of the therapeutic approaches to asthma is to inhibit activation of cells involved in hypersensitivity reactions. Nedocromil sodium is a new drug undergoing clinical evaluation for the treatment of asthma. Like sodium cromoglycate it induces phosphorylation of a 78000 m.wt. protein in the rat peritoneal mast cell (Stevenson *et al.*, 1983). Both compounds stabilize rat peritoneal mast cells but they differ markedly in their ability to inhibit mucosal mast cells, nedocromil sodium being the more active (Wells *et al.*, 1986). Both drugs have been shown to be effective in inhibition of IgE-dependent stimulation of cells bearing the $Fc_{epsilon}$ R_{II} receptor (especially macrophages, eosinophils and platelets) (Kay, 1986; Riley *et al.*, 1986; Spry *et al.*, 1986; Thorel *et al.*, 1988; Tsicopoulos *et al.*, 1987) as well as in inhibition of neutrophils (Bradford & Rubin, 1986). We therefore investigated their possible activity in ASA.

It has been previously established that, *in vitro*, sodium cromoglycate and nedocromil sodium could modulate platelet responsiveness to aspirin in aspirin-sensitive patients (Thorel *et al.*, 1987). At maximal effect of sodium cromoglycate, nedocromil sodium was 500 times more potent in inhibiting aspirin-induced activation of platelets. For this reason it was decided to test the effect of nedocromil sodium in aspirin-sensitive patients.

Inhalation of a single dose of 4 mg of nedocromil sodium provided by a metered dose inhaler resulted in a dramatic (70.8 ± 8.18%) inhibition of platelet responsiveness to aspirin. This inhibition occurred soon after nedocromil sodium intake (15 min) in all patients but two. In these two patients strong inhibition (83.15 ± 1.85%) was observed at 60 min. One hour after nedocromil sodium inhalation, inhibition was even more frank (86.5 ± 4.60%) in all patients. The effect of nedocromil sodium then progressively decreased with time: the mean inhibition was 72.7%; 57.2%; 47.0% and 17.0%

respectively at $t120$, $t180$, $t360$, $t480$. On day 7, the aspirin-dependent platelet cytotoxicity assay was performed early in the morning (≈ 09.00 h), approximately 12 h after the last nedocromil sodium intake. The platelet response to aspirin was similar to that observed on day 1, before any nedocromil sodium intake, in all patients but two. Thus, there does not appear to be residual effect at 12 h, nor a cumulative effect, in spite of a steady intake of the drug four times a day during 1 week. One of the patients, whose platelets had stopped responding to aspirin had a detectable trough level of nedocromil sodium (0.3 ng ml^{-1}), although the possibility of an inhalation early in the morning could not be ruled out. In the other patient the drug could not be detected in the plasma, and persistence of a residual inhibitory effect of nedocromil sodium is a likely explanation.

Peak plasma concentrations of nedocromil sodium were within the limits reported by pharmacological studies (Auty & Clarke, 1986). Linear correlation between the plasma concentration and the degree of plasma inhibition could not be defined. However, the comparison between the time-dependent platelet inhibition after inhalation and the pharmacokinetics of the drug after inhalation suggested a dose dependent response.

The nature of the interaction between nedocromil sodium and platelet metabolism is not yet clear. Therefore it was noteworthy to study *'ex vivo'* platelet reactivity following nedocromil sodium inhalation independently of the potential inhibitory effect of the corresponding serum (containing nedocromil sodium). Even when incubated with 'nedocromil sodium free serum' and two washings, platelet reactivity to aspirin dramatically dropped at 15 and 60 min. This suggests that (1) nedocromil sodium is likely to bind strongly and rapidly to a receptor on platelets; and (2) nedocromil sodium induces very rapid changes in platelet metabolism, preventing them from subsequent activation by aspirin. These two hypotheses are not mutually exclusive. These results also permit us to rule out a scavenger effect of nedocromil sodium on the metabolites of platelet activation or on aspirin directly.

Finally it is noteworthy that nedocromil sodium was able to inhibit the only cell which has been shown to react to aspirin in ASA. However, this does not prejudge the efficacy of nedocromil sodium in treating aspirin-sensitive asthmatics. Further clinical studies will be necessary to establish the efficacy of this drug in aspirin intolerance.

References

Ameisen, J. C. (1986). Aspirin-sensitive asthma, a model for a role of platelets in hypersensitivity reactions. *Ann. Inst. Pasteur/Immunol.*, **137D**, 141–147.

Ameisen, J. C., Capron, A., Joseph, M., Maclouf, J., Vorng, H., Pancre, V., Fournier, E., Wallaert, B. & Tonnel, A. B. (1985). Aspirin sensitive asthma, abnormal platelet response to drugs inducing asthmatic attacks. Diagnostic and physiological implications. *Int. Archs. Allergy appl. Immunol.*, **78**, 438–448.

Ameisen, J. C., Capron, A., Joseph, M. & Tonnel, A. B. (1986a). Platelets and aspirin induced asthma. In *Asthma: Clinical pharmacology and therapeutic progress*, ed. Kay, A. B., pp.226–236. Oxford: Blackwell.

Ameisen, J. C., Fournier, E., Vorng, H., Tonnel, A. B., Joseph, M. & Capron, A. (1986b). Serum from aspirin desensitized patients inhibits the abnormal response to NSAIDs. *J. Allergy clin. Immunol.*, **77**, 182 (abstract).

Ameisen, J. C., Martinot, J. B., Tonnel, A. B., Maclouf, J., Joseph, M., Vargafting, B. & Capron, A. (1986c). Aspirin sensitive asthma: role of endoperoxide receptor in the abnormal platelet response to NSAIDs. Abstract Book. *6th Int. Congr. Immunol.*, Toronto, 660

Auty, R. M. & Clarke, A. J. (1986). Kinetics and disposition of nedocromil sodium in man: preliminary report. *Eur. J. resp. Dis.*, **69**, (Suppl. 147), 246–247.

Baldocchi, G., Vervloet, D. & Charpin, J. (1983). Acetyl-salicylic therapy in aspirin sensitive asthmatics. *J. Allergy. clin. Immunol.*, **71**, 148 (abstract).

Basomba, A., Romar, A., Pelaez, A., Villalmanzo, I. G. & Campos, A. (1976). The effect of sodium cromoglycate in preventing aspirin induced bronchospasm. *Clin. Allergy*, **6**, 269–275.

Bradford, P. G. & Rubin, R. P. (1986). The differential effects of nedocromil sodium and sodium cromoglycate on the secretory response of rabbit peritoneal neutrophils. *Eur. J. resp. Dis.*, **69**, (suppl 147), 238–240.

Capron, A., Dessaint, J. P., Capron, M., Ameisen, J. C. & Tonnel, A. B. (1986). From parasites to allergy: a second receptor for IgE. *Immunology Today*, **7**, 15–18.

Capron, A., Joseph, M., Ameisen, J. C., Capron, M., Pancre, V. & Auriault, C. (1987). Platelets as effectors in immune and hypersensitivity reactions. *Int. Archs. Allergy appl. Immunol.*, **82**, 307–312.

Danker, R. E. & Wedner, H. J. (1983). Aspirin desensitization in aspirin-sensitive asthma, failure to

obtain a desensitized state during prolonged therapy. *Am. Rev. resp. Dis.*, **128**, 953–955.

Delaney, J. C. (1976). The effect of sodium cromoglycate on analgesic-induced asthmatic reactions. *Clin. Allergy*, **6**, 365–368.

Delaney, J. C. (1983). The effect of ketotifen on aspirin-induced asthmatic reactions. *Clin. Allergy*, **13**, 247–251.

Johnson, C. E., Belfield, P. W., Davis, S., Cooke, N. J., Spencer, A. & Davies, J. A. (1986). Platelet activation during exercise induced asthma: effect of prophylaxis with cromoglycate and salbutamol. *Thorax*, **41**, 290–294.

Kay, A. B. (1986). Mediators and inflammatory cells in asthma. In *Asthma: Clinical pharmacology and therapeutic progress*, ed. Kay, A. B., pp 1–10. Oxford: Blackwell.

Martin, B. G. & Culver, W. G. (1983). Failure to desensitize an aspirin-sensitive asthmatic on two aspirin desensitization attempts. Aspirin desensitization in aspirin-sensitive asthma. *J. Allergy. clin. Immunol.*, **71**, 148 (abstract).

Metzger, W. J., Hunninghake, G. W. & Richerson, H. B. (1985). Late asthmatic responses: Inquiry into mechanisms and significance. *Clin. Rev. Allergy*, **3**, 145–165.

Pleskow, W. W., Stevenson, D. D., Mathison, D. A., Simon, R. A., Schatz, M. & Zeiger, R. S. (1982). Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical presentation and characterization of the refractory period. *J. Allergy. clin. Immunol.*, **69**, 11–19.

Riley, P. A., Mather, M. A., Keogh, R. W. & Eady, R. P. (1986). Activity of nedocromil sodium in mast-cell dependent reactions in the rat. *Int. Archs. Allergy appl. Immunol.*, **82**, 108–110.

Slepian, I. K., Kennet, P. M. & McLean, J. A. (1985). Aspirin sensitive asthma. Chest, **87**, 386–391.

Spector, S. L. & Farr, R. S. (1983). Aspirin idiosyncrasy. In *Allergy Principles and Practice*, eds Middleton, E., Reed, C. E. & Ellis, E. F. pp. 1249–1273. St. Louis: Mosby.

Spry, C. J., Kumaraswami, V. & Tai, P. C. (1986). The effect of nedocromil sodium in secretion from human eosinophils. *Eur. J. resp. Dis.*, **69** (suppl 147), 241–243.

Stevenson, D. D., Pleskow, W. W., Simon, R. A., Mathison, D. A., Lumry, W. R. & Schatz, M. (1983). Treatment of aspirin sensitive asthma/rhinosinusitis with aspirin. *J. Allergy clin. Immunol.*, **71**, 156 (abstract).

Szczeklik, A., Czerniawska-Mysik, G., Serwonska, M. & Kuklinski. P. (1980). Inhibition by ketotifen of idiosyncratic reactions to aspirin. *Allergy*, **35**, 421–424.

Szczeklik, A., Gryglewski, R. J. & Czerniawska-Mysik, G. (1983). Clinical patterns of hypersensitivity to non steroidal anti-inflammatory drugs and their pathogenesis. *Drugs*, **25**, 533–543.

Thorel, T., Ameisen, J. C., Joseph, M., Vorng, H., Tonnel, A. B., Marquette, C. H. & Capron, A. (1987). Preventing effect of nedocromil sodium on the abnormal response to aspirin of platelets from aspirin-sensitive asthmatics. *Am. Rev. resp. Dis.*, **135**, A398.

Thorel, T., Joseph, M., Tsicopoulos, A., Tonnel, A. B. & Capron, A. (1988a). Inhibition by nedocromil sodium of the IgE mediated activation of human mononuclear phagocytes and platelets in allergy. *Int. Archs. Allergy appl. Immunol.*, **85**, 232–237.

Thorel, T., Joseph, M., Vorng, H. & Capron, A. (1988b). Regulation of IgE-dependent antiparasite functions of rat macrophages and platelets by nedocromil sodium. *Int. Archs. Allergy appl. Immunol.*, **85**, 227–231.

Tsicopoulos, A., Lassalle, P., Joseph, M., Tonnel, A. B., Thorel, T., Dessaint, J. P. & Capron, A. (1987). Effect of disodium cromoglycate on inflammatory cells bearing the Fc epsilon receptor type II (Fc_eRII). *Int. J. Immunopharmac.*, **10**, 227–236.

Wells, E., Jackson, C. G., Harper, S. T., Mann, J. & Eady, R. P. (1986). Characterization of primate bronchoalveolar mast cells II. Inhibition of histamine, LTC_4 and PGD_2 release from primate bronchoalveolar mast cells and a comparison with rat peritoneal mast cells. *J. Immunol.*, **137**, 3941–3945.

(Received 21 October 1988, accepted 3 October 1989)